Original Article

Identification of Key Genes Associated with Polycystic Ovarian Syndrome and Endometrial and Ovarian Cancer through Bioinformatics

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Abstract

Background: Polycystic ovary syndrome (PCOS), a common endocrine disorder, is linked to increased risks of endometrial cancer (EC) and ovarian cancer (OC). Our study utilises bioinformatics analysis to identify shared gene signatures and elucidate biological processes between EC and OC and PCOS. **Aim:** The objective of this research is to unveil the common molecular landscape shared by PCOS and EC and OC. **Settings and Design:** An observational computational bioinformatics analysis. **Materials and Methods:** Gene expression profiles for PCOS (GSE199225), EC (GSE215413) and OC (GSE174670) were obtained from the Gene Expression Omnibus database. Hub genes were identified through functional enrichment analysis and protein–protein interaction. Drug identification analyses were employed to find drugs targeting the hub genes. **Results:** Key hub genes linking PCOS and EC includes *RECQL4*, *RAD54L*, *ATR*, *CHTF18*, *WDHD1*, *CDT1*, *PLK1*, *PKMYT1*, *RAD18* and *RPL3*; for PCOS and OC, they include *HMOX1*, *TXNRD1*, *NQO1*, *GCLC*, *GSTP1*, *PRDX1*, *SOD1*, *GPX3*, *BOP1* and *BYSL*. Gene Ontology analysis revealed DNA metabolic process in PCOS and EC, while in PCOS and OC, it identified the removal of superoxide radicals. Kyoto Encyclopaedia of Genes and Genomes pathway analysis highlighted cell cycle in PCOS and EC and hepatocellular carcinoma in PCOS and OC. Potential drugs for PCOS and EC include quercetin, calcitriol and testosterone; for PCOS and OC, eugenol and 1-chloro-2,4-dinitrobenzene are identified. **Conclusion:** These findings offer insights into potential therapeutic targets and pathways linking PCOS with EC and OC, enhancing our understanding of the molecular mechanisms involved in these associations.

Keywords: *Bioinformatics, endometrial cancer, ovarian cancer, polycystic ovary syndrome*

Introduction

Polycystic ovary syndrome (PCOS) impacts around 5%–10% of women in their reproductive years, emerging as the leading cause of anovulation amongst those facing infertility. Its onset is gradual, presenting a clinical spectrum that encompasses the classic triad of PCOS symptoms: hyperandrogenism, menstrual irregularities and the presence of polycystic ovaries.[1]

A polycystic ovary detected by ultrasound, infertility, acne, amenorrhea or oligomenorrhoea, hirsutism, insulin resistance (IR), obesity and hyperandrogenism can all be indicators of PCOS.[2] In addition to reproductive irregularities, a variety of metabolic illnesses, including hypertension, hepatic steatosis, glucose intolerance, dyslipidaemia and type II diabetes, are significantly

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linked to PCOS. In the development of PCOS, hyaluronic acid (HA) plays a crucial role in fostering ovulatory dysfunction. It induces abnormalities in lipid metabolism, encourages hyperinsulinaemia and IR, disrupts the luteinising hormone (LH) to follicle-stimulating hormone ratio and raises the frequency and intensity of LH and gonadotropin-releasing hormone pulse secretion. Studies have suggested that these factors possess the capacity to directly stimulate the proliferation of cancer cells.[3]

Studies have established a connection between PCOS and cancers affecting the endometrium, ovaries, kidneys, haematological system and pancreas. Progress in comprehending the molecular processes involved in PCOS has facilitated these discoveries.[4]

Endometrial cancer (EC) is a major gynaecological concern, prevalent in the Western world and a significant cause of mortality. It affects the inner lining of the uterus, with a globally increasing incidence. Meta-analyses highlight PCOS as a notable risk factor, with women having PCOS being three times more likely to develop EC. The risk is significantly higher for women under 54 compared to older individuals.[5] The primary hypotheses seeking to elucidate the connection between PCOS and EC involve elevated oestrogen levels, hyperinsulinaemia, progesterone resistance and decreased apoptosis in women. These factors contribute to the development of endometrial hyperplasia, ultimately leading to the onset of EC.[6]

Ovarian cancer (OC) currently ranks as the fifth leading cause of cancer-related deaths amongst women in the United States, and approximately 140,000 women globally succumb to OC each year.[7] Research examining the association between OC and PCOS has been conducted, with a notable study by Schildkraut *et al*.[8] reporting a 2.5-fold risk of OC in women with PCOS, which increased to a 10.5-fold risk in those not using oral contraceptives. In contrast, most studies exploring the correlation between PCOS and OC have not been able to establish a clear link. An exception is a study by Rossing *et al*.,[9] which investigated connections amongst infertility, OC and ovulation-inducing drugs. This research suggested a 2.3-fold risk of OC associated with clomiphene treatment in these women, a finding supported by subsequent studies.[10] Examining the molecular mechanisms of PCOS that elevate the susceptibility to endometrial and OC s can provide insights into the pathogenesis of these conditions through bioinformatics data analysis.

Our analysis adopts a more comprehensive approach than Smith and Johnson's, who concentrated exclusively on PCOS and OC, and Brown and White, who similarly focussed on identifying shared gene signatures between PCOS and EC.[11,12]

By examining common gene signatures and pathways amongst various gynaecological malignancies, our research goes beyond particular disease relationships and provides a more comprehensive understanding of the relationship between PCOS and the development of cancer. The objective of our research is to identify shared molecular pathways that could be dysregulated in the context of PCOS's hormonal dysregulation by comparing the gene expression profiles of various gynaecological cancers.

This study aims to identify the differentially expressed genes (DEGs), pathways and protein networks shared between PCOS and endometrial and OCs. In addition, it seeks to identify potential targeted therapeutic approaches by assessing common genetic factors identified in PCOS and endometrial and OC. The findings may open up new avenues for therapeutic strategies, offering innovative possibilities for treatment.

Materials and Methods

Study design

In this study, subjects diagnosed with PCOS, EC and OC were compared with respective normal subjects. The data were obtained from publicly available databases hosted by National Center for Biotechnology Information (NCBI). Gene profile data were retrieved and utilised to identify DEGs between PCOS and EC, as well as between PCOS and OC, using the GEO2R online tool. A significance threshold of adjusted $P < 0.05$ was applied to the data. Venn diagrams were then generated using the VENNY2.1 web tool to visualise the identified DEGs. Subsequently, the DEGs were subjected to protein–protein interaction (PPI) analysis using the Search Tool for the Retrieval of Interacting Gene (STRING) tool, and the resulting network was visualised using Cytoscape. Hub genes within the PPI network were identified using the CytoHubba plugin based on the maximal clique centrality algorithm. Functional enrichment analysis of the identified hub genes was performed using Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) databases to elucidate key biological processes and pathways associated with the hub genes. In addition, potential drug targets against the hub genes were identified using the DSigDB online platform. The protocol for this study aligns with previously published methodologies referenced in relevant literature.[11-13]

Ethical approval

The study is based on the analysis of anonymised, publicly accessible genetic or clinical databases that do not contain personal patient data. These datasets are freely available and sourced properly. The core of our work is bioinformatics analysis, which applies computational methods to these pre-existing datasets without requiring fresh data collection from subjects. Consequently, potential ethical concerns regarding participant consent, privacy and confidentiality are mitigated. Given their pre-existing nature, there is no direct interaction with human subjects, thereby circumventing the necessity for ethical committee approval.

Data retrieval

We obtained microarray datasets from the NCBI Gene Expression Omnibus (GEO) to investigate the impact of PCOS and its genetic associations with endometrial and OC. The GEO is a comprehensive and freely accessible database (www.ncbi.nlm.nih.gov/geo) that offers gene expression profiles for various disorders.[14]

For our study, we analysed three distinct microarray datasets from the GEO database hosted by the NCBI. These datasets corresponded to PCOS, EC and OC, identified by the accession numbers GSE199225,[15] GSE215413[16] and GSE174670,[17] respectively. Our selection criteria included considering only complete samples categorised as either cases or controls. Non-human datasets were excluded, and exclusively human data were utilised.

In the PCOS datasets, our cases comprised skeletal muscle samples obtained from women diagnosed with PCOS, while controls consisted of skeletal muscle samples from unaffected, healthy women. This comparison allowed us to elucidate gene expression differences associated with PCOS pathogenesis, particularly in skeletal muscle, a tissue crucial for metabolic function and exercise response. Moving to the EC datasets, our cases involved EC cell lines with LIM1 knockdown, aiming to explore the specific role of LIM1 in cancer progression. These cases were compared against controls consisting of EC cell lines treated with control shRNA. Finally, in our OC datasets, we examined OC cell lines treated with BET inhibitors as cases, contrasting them with untreated control cell lines.

Identification of shared differentially expressed genes in polycystic ovary syndrome and endometrial and ovarian cancer

To pinpoint shared DEGs between PCOS and endometrial and OC, the online tool GEO2R (www.ncbi.nlm.nih.gov/geo/geo2r/) was employed for group comparison and analysis, offering a user-friendly interface for differential expression analysis.[18] GEO2R facilitates the comparison of gene expression across different experimental conditions within a GEO series. It integrates DESeq2 for RNA-seq data and GEO query with limma for microarray data, providing a comprehensive platform for researchers to conduct differential expression analysis and visualise results with high-throughput genomic data.

The datasets GSE199225, GSE215413 and GSE174670 were subjected to GEO2R analysis to identify DEGs, defined as genes with |log2 fold change (log2FC) |>1.0 and an adjusted $P < 0.05$. GEO2R not only presents results in a table of genes ordered by P value but also offers graphic plots for visualising DEGs and assessing data set quality. Volcano plots of DEGs from each dataset were obtained through GEO2R analysis, offering a visual representation of statistical significance (−log10 P value) versus the magnitude of change (log2 fold change).

Common DEGs between GSE199225 and GSE215413, as well as GSE199225 and GSE174670 datasets, were identified using GEO2R and visualised using the Venny v2.1 web tool.[19] These common DEGs were considered potential genes associated with the risk of endometrial and OC in women with PCOS.

Analysis of protein–protein interaction networks and the identification of hub genes

The evaluation of PPI networks is fundamental in cellular biology for comprehending protein function and the workings of cellular machinery. The STRINGs (http://string-db.org) are a database designed for the study of PPI networks, incorporating both physical and functional interactions.[20] In our study, we utilised STRING to construct the PPI network of shared DEGs, focussing on interactions with a score exceeding 0.4. The resulting network was visualised using Cytoscape (Version 3.9.1).[21]

The hub genes of this study were identified using CytoHubba77, a plug-in of Cytoscape.[22]

Hub genes were selected mainly based on their Maximal Clique Centrality (MCC) algorithm, which indicates the essentiality of nodes in biological network.

Functional enrichment analysis

Enrichment analysis of hub genes involved the utilisation of the Enrichr web-based tool.[23] This tool was employed for GO and KEGG enrichment analysis, aiming to elucidate the biological functions and signalling pathways associated with the identified hub genes. The analysis encompassed gene ontologies

related to biological processes, cellular components and molecular functions. In addition, for the exploration of signalling pathways, databases such as Reactome (2022), KEGG pathways (2021) and WikiPathways (2023) were investigated.

To establish significance, a statistical threshold criterion of $P < 0.05$ was applied for the selection of enriched GO terms and pathways.

Prediction of candidate drugs

The DSigDB database, comprising 19,531 genes and 17,389 compounds, serves as a valuable resource facilitating a direct link between genes and drugs, particularly in the context of drug development studies and translational research.[24] Accessible through the Enrichr web server (https://amp.pharm.mssm.edu/Enrichr/), the DSigDB database is utilised for analysing the relationship between drugs and potential targets. In our study, hub genes were submitted to the database to identify potential drug molecules targeting these genes. Subsequently, compounds were ranked based on the adjusted $P < 0.05$ and the combined score, calculated using the P value and z-score by assessing the deviation from the expected rank.[25]

Results

Identification of differentially expressed genes and common genes

The GSE199225 data set includes 31 normal skeletal muscle biopsy samples and 30 case skeletal muscle biopsy samples of women affected with PCOS. Figure 1a shows the results of the differential analysis of the GSE199225 data set, including 2195 DEGs, 2044 downregulated genes and 151 upregulated genes. GSE215413 contains two control human endometrium cancer cell lines and nine case LIM1-knocked down human endometrium cancer cell lines. Figure 1b shows the results of the differential analysis of the GSE215413 data set, including 3136 DEGs, 2795 downregulated genes and 341 upregulated genes.

GSE174670 datasets contains 6 control samples and 12 case samples for the study. Figure 1c shows the results of the differential analysis of the GSE174670 data set, including 6724 DEGs, 5415 downregulated

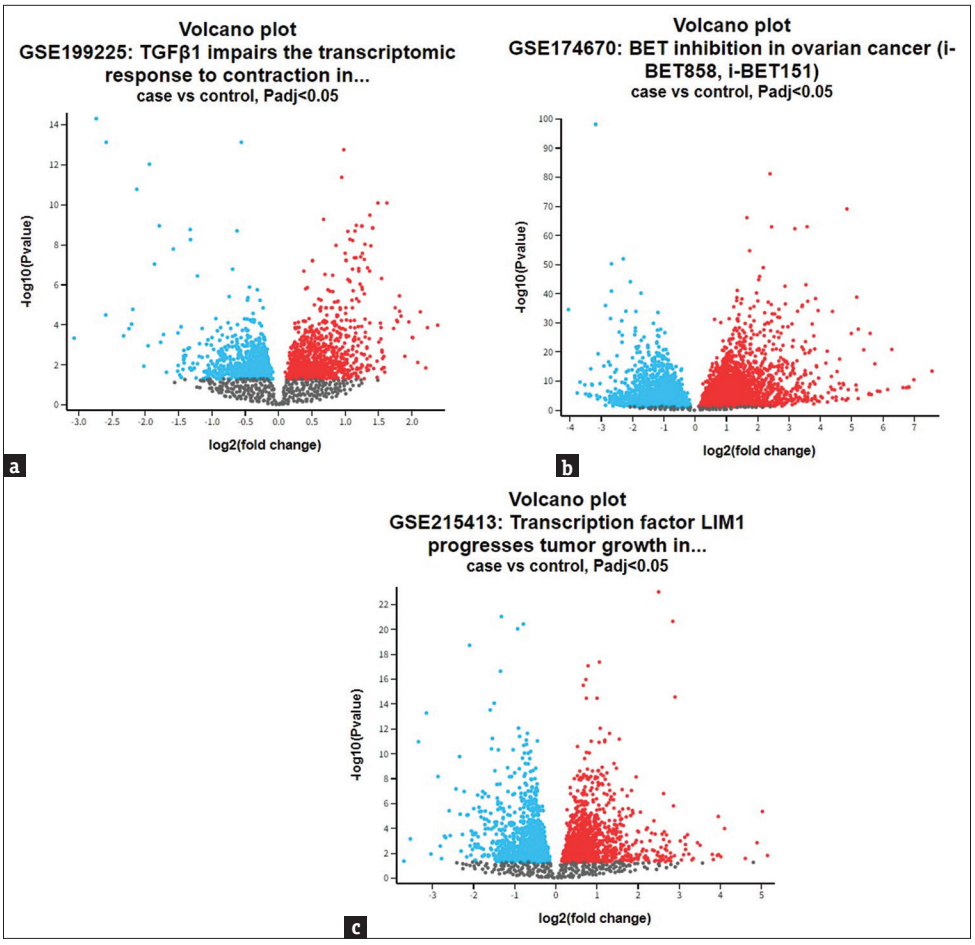

Figure 1: (a) Volcano map of differential genes in the GSE199225 data set. The red colour represents upregulated genes and blue are downregulated genes, (b) Volcano map of differential genes in the GSE215413 data set, (c) Volcano map of differential genes in the GSE174670

genes and 1309 upregulated genes. The detail of the included datasets is shown in Table 1.

The Venn diagram visualisation revealed 344 genes shared between PCOS and EC [Figure 2a], and 716 genes common to both PCOS and OC [Figure 2b].

Analysis of the protein–protein interaction network and the identification of hub genes

The PPI network analysis of 344 common DEGs between PCOS and EC and 716 common DEGs between PCOS and OC was conducted using the STRING platform, with a medium confidence threshold (score >0.4) for constructing the PPI network. The results were visualised using Cytoscape software. Subsequently, the top 10 hub genes were identified through the implementation of 11 algorithms from the CytoHubba plug-in in Cytoscape. The maximal clique centrality (MCC) algorithm was specifically employed to identify the top 10 hub nodes, with the ranking visualised using a red-to-yellow colour gradient.

The top 10 hub genes associated with PCOS and EC include *RECQL4*, *RAD54L, ATR, CHTF18, WDHD1, CDT1, PLK1, PKMYT1, RAD18* and *RPL3* [Table 2]. The network comprised 10 nodes and 35 edges [Figure 3a].

Similarly, the top 10 hub genes associated with PCOS and OC include *HMOX1*, *TXNRD1, NQO1, GCLC, GSTP1,*

Table 1: Detailed information of the selected microarray data

Disease	GEO number	Control sample	Case sample	Significant genes	Upregulated genes	Downregulated genes
PCOS	GSE199225	31	30	2195	151	2044
EC	GSE215413	2	9	3136	341	2795
OC	GSE174670	6	12	6724	1309	5415

GEO=Gene Expression Omnibus, PCOS=Polycystic ovary syndrome, EC=Endometrial cancer, OC=Ovarian cancer

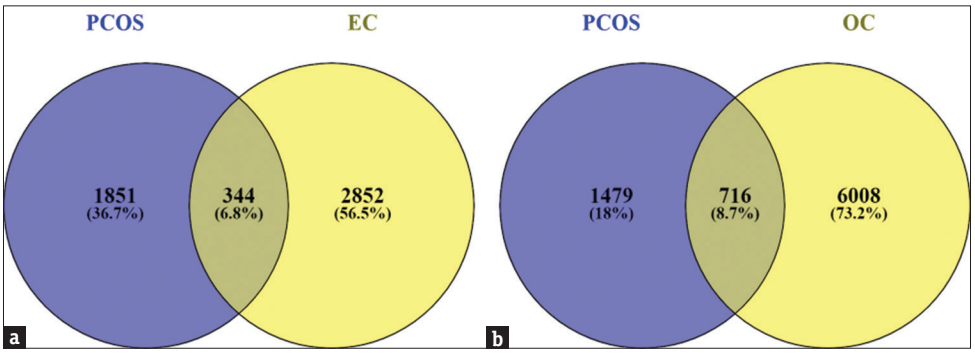

Figure 2: (a) Venn diagram of the intersections of polycystic ovary syndrome (PCOS) and endometrial cancer (EC). Intersections represent the differentially expressed genes (DEGs) in PCOS-associated data series and EC-associated data series (b) Venn diagram of the intersections of PCOS and ovarian cancer (OC). Intersections represent the DEGs in PCOS-associated data series and OC-associated data series. PCOS = Polycystic ovary syndrome, EC = Endometrial cancer, OC = Ovarian cancer

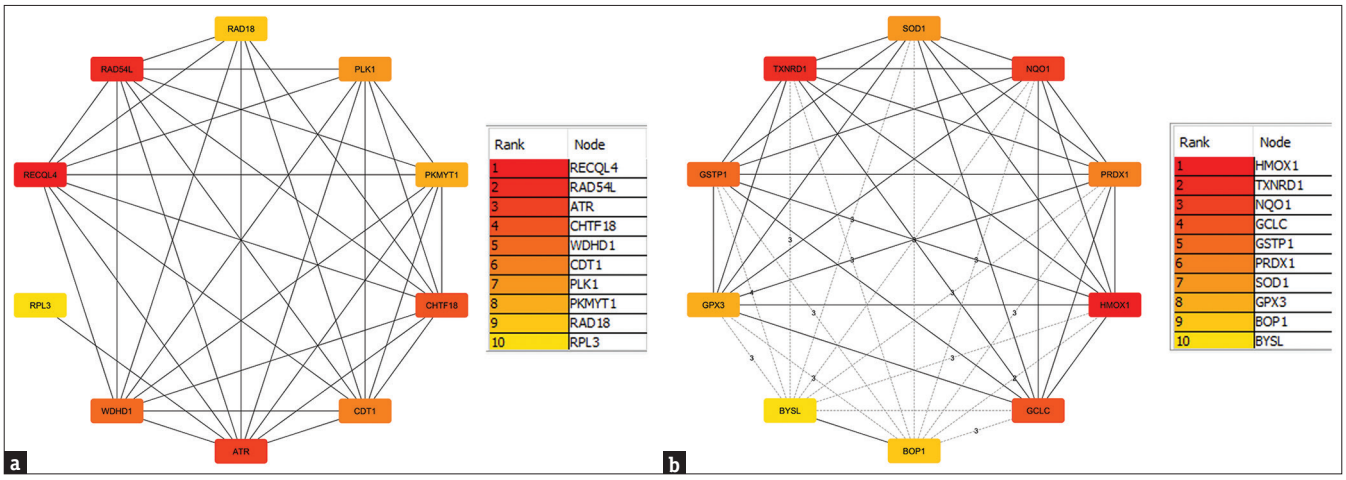

Figure 3: Hub genes screening. The colour of the nodes is illustrated from red to yellow in descending order of MCC score. Grey lines highlight the interactions; line thickness refers to the interaction score provided by Search Tool for the Retrieval of Interacting Gene. The redder the colour of the gene in the network, the higher the connectivity of the gene with other genes. (a) Hub genes of Polycystic Ovary Syndrome (PCOS) and endometrial cancer (b) Hub genes of PCOS and ovarian cancer

Table 2: Hub genes identified through protein–protein interaction analysis

Hub genes	MCC score	Description
PCOS and EC		
RECQL4	6840	RecQ like helicase 4
RAD54L	6828	RAD54 like
ATR	6671	ATR serine/threonine kinase
CHTF18	6606	Chromosome transmission fidelity factor 18
WDHD1	6600	WD repeat and HMG-box DNA binding protein 1
CDT1	6062	Chromatin licensing and DNA replication factor 1
PLK1	5262	Polo-like kinase 1
PKMYT1	5162	Protein kinase, membrane-associated tyrosine/threonine 1
RAD18	1764	RAD18 E3 ubiquitin protein ligase
RPL3	1024	Ribosomal protein L3
PCOS and OC		
HMOX1	5362	Heme oxygenase 1
TXNRD1	5347	Thioredoxin reductase 1
NQO1	5311	NAD (P) H quinone dehydrogenase 1
GCLC	5305	Glutamate-cysteine ligase catalytic subunit
GSTP1	5194	Glutathione S-transferase pi 1
PRDX1	5177	Peroxiredoxin 1
SOD1	5113	Superoxide dismutase 1
GPX3	5089	Glutathione peroxidase 3
BOP1	1725	BOP1 ribosomal biogenesis factor
BYSL	1720	Bystin like

MCC scores indicated the essentiality of the gene in biological network. The greater the value, the more important the gene. MCC=Maximal clique centrality, PCOS=Polycystic ovary syndrome, EC=Endometrial cancer, OC=Ovarian cancer

PRDX1, SOD1, GPX3, BOP1 and *BYSL* [Table 2]. The network for this association consisted of 10 nodes and 45 edges [Figure 3b].

Pathway and functional enrichment analysis

A diverse array of signalling pathways and GO terms play a crucial role in the orchestration and development of diseases, especially in complex disorders. To analyse the GO and pathway enrichment of the Hub genes, we utilised the Enrichr online tool. The significance of terms was determined based on the *P* value. The GO analysis comprised three categories: biological process (2023), cellular component (2023) and molecular function (2023). The top 10 significant terms from each category are summarised in Tables 3 and 4 and presented as bar graphs in Supplementary Figures 1 and 2.

This analysis helped identify key pathways and gene ontologies that could establish connections between PCOS and endometrial and OC using hub genes.

Furthermore, we identified the most impacted pathways of the common DEGs amongst EBV infection, SLE and DLBCL from four databases (WikiPathway, Reactome and KEGG). The top 10 pathways from these datasets are compiled in Tables 5 and 6 and illustrated in bar graphs in Supplementary Figures 3 and 4.

This analysis helped identify key pathways and gene ontologies that could establish connections between PCOS and EC/OC using hub genes.

Prediction of drug candidate

Utilising the Enrichr platform, which is based on the DSigDB database, we identified and ranked the top 10 potential therapeutic compounds based on their *P* values in relation to hub genes. These compounds were considered promising pharmacological targets for PCOS and EC [Table 7] and PCOS and OC [Table 8].

Notably, three pharmacological molecules – testosterone (CTD 00006844), calcitriol (CTD 00005558) and quercetin (CTD 00006679) – were found to interact with the majority of genes in the PCOS and EC context. In the case of PCOS and OC, the two drugs that interacted with most of the genes were 1-chloro-2,4-dinitrobenzene (CTD 00005848) and eugenol (CTD 00005949).

Discussion

Several studies have suggested an elevated risk of endometrial and OC in women with PCOS, indicating a potential link between PCOS, EC and OC. However, the underlying mechanisms remain unclear.

In this study, a series of bioinformatics analyses were conducted to identify hub genes associated with PCOS

Table 3: Ontological analysis of hub genes between polycystic ovary syndrome and endometrial cancer

Category	GO ID	Term	*P*	Genes
GO - biological process	GO:0006259	DNA metabolic process	0.000008259	RECQL4, WDHD1, RAD18, ATR
	GO:0006281	DNA repair	0.000008604	RECQL4, WDHD1, RAD18, ATR
	GO:0006974	DNA damage response	0.00002564	RECQL4, WDHD1, RAD18, ATR
	GO:0000086	G2/M transition of mitotic cell cycle	0.0001567	PLK1, PKMYT1
	GO:0044839	Cell cycle G2/M phase transition	0.0001737	PLK1, PKMYT1
	GO:0034502	Protein localisation to chromosome	0.0001737	PLK1, ATR
	GO:0031570	DNA integrity checkpoint signalling	0.0001917	CDT1, ATR
	GO:0032200	Telomere organisation	0.0004323	RECQL4, ATR
GO - cellular component	GO:0043232	Intracellular non-membrane-bounded organelle	0.0001477	RECQL4, RPL3, PLK1, PKMYT1, ATR
	GO:0005634	Nucleus	0.001782	RECQL4, CDT1, RPL3, PLK1, CHTF18, RAD18, ATR
	GO:0005694	Chromosome	0.002880	RECQL4, ATR
	GO:0043231	Intracellular membrane-bounded organelle	0.004322	RECQL4, CDT1, RPL3, PLKT1, CHTF18, RAD18, ATR
	GO:0042405	Nuclear inclusion body	0.004990	RAD18
	GO:0022625	Cytosolic large ribosomal subunit	0.02570	RPL3
	GO:0015934	Large ribosomal subunit	0.02570	RPL3
	GO:0005876	Spindle microtubule	0.03349	PLK1
GO - molecular function	GO:0000217	DNA secondary structure binding	0.0001178	RECQL4, RAD18
	GO:0004674	Protein serine/threonine kinase activity	0.0005440	PLK1, PKMYT1, ATR
	GO:0009378	Four-way junction helicase activity	0.002498	RECQL4
	GO:0140666	Annealing activity	0.002498	RECQL4
	GO:0032356	Oxidised DNA binding	0.003495	RECQL4
	GO:0000405	Bubble DNA binding	0.003495	RECQL4
	GO:0032357	Oxidised purine DNA binding	0.004492	RECQL4
	GO:0043138	3'-5' DNA helicase activity	0.006979	RECQL4

GO=Gene Ontology

and EC/OC. A total of 10 hub genes were identified from the DEGs in PCOS and EC, including *RECQL4, RAD54L, ATR, CHTF18, WDHD1, CDT1, PLK1, PKMYT1, RAD18* and *RPL3*. Similarly, another set of 10 hub genes emerged from the DEGs in PCOS and OC, including *HMOX1, TXNRD1*, *NQO1, GCLC, GSTP1, PRDX1, SOD1, GPX3, BOP1* and *BYSL*.

GO analysis was performed using the 20 hub genes identified across the three datasets of PCOS, EC and OC. Noteworthy biological processes in the GO analysis of PCOS and EC included DNA metabolic process, DNA repair and DNA damage response. Conversely, in the GO analysis of PCOS and OC, significant processes included removal of superoxide radicals, cellular response to superoxide and superoxide metabolic process.

DNA damage response and repair pathways are implicated in EC development.[26] Increased expression of obesity-associated genes in women with PCOS may contribute to EC progression.[27] PCOS, marked by endocrine and metabolic disruptions, often accompanies oxidative stress. Addressing internal oxidative stress could be a potential therapeutic strategy.[28] Reactive oxygen species (ROS) play a key role in signalling, but excessive or prolonged ROS production is linked to cancer initiation and progression.[29] Oxidative stress is implicated in the onset of OC.[30] Superoxide dismutases (SODs), enzymes responsible for neutralising superoxide free radicals, play vital roles in cancer cell development, growth and survival.[31]

KEGG pathway enrichment analysis unveiled that the most significant pathways in the context of PCOS and EC include cell cycle, progesterone-mediated oocyte maturation and oocyte meiosis. Dysregulation of key cell cycle regulators, such as cyclin B1, cyclin D1, cyclin E, p16, p21, p27, p53 and cdk2, is crucial in EC progression.[32] Progesterone, vital for oocyte maturation and embryo development, has significant effects *in vitro* and *in vivo*, with conflicting results.[33] Acting through progesterone receptor isoform A (PR-A) and PR-B, progesterone plays a crucial role in uterine physiology, regulating development, implantation and acting as a tumour suppressor in EC cells.[34] Elevated mRNA instability index in uterine corpus endometrial carcinoma correlates with reduced overall survival, possibly involving oocyte meiosis and cell cycle pathways.[35]

In the case of PCOS and OC, the top three significant pathways identified through KEGG pathway

Table 4: Ontological analysis of hub genes between polycystic ovary syndrome and ovarian cancer

Category	GO ID	Term	*P*	Genes
GO - biological process	GO:0019430	Removal of superoxide radicals	1.078e-8	NQO1, PRDX1, SOD1
	GO:0071451	Cellular response to superoxide	1.482e-8	NQO1, PRDX1, SOD1
	GO:0006801	Superoxide metabolic process	5.342e-7	NQO1, PRDX1, SOD1
	GO:0000302	Response to ROS	0.000004051	GSTP1, HMOX1, SOD1
	GO:0032930	Positive regulation of superoxide anion generation	0.00001750	GSTP1, SOD1
	GO:0032928	Regulation of superoxide anion generation	0.00002041	GSTP1, SOD1
	GO:0042744	Hydrogen peroxide catabolic process	0.00004255	GPX3, PRDX1
	GO:0001895	Retina homeostasis	0.0001651	PRDX1, SOD1
GO - cellular component	GO:0005694	Chromosome	0.002880	BOP1, BYSL
	GO:0032839	Dendrite cytoplasm	0.003994	SOD1
	GO:0120111	Neuron projection cytoplasm	0.004990	SOD1
	GO:0005758	Mitochondrial intermembrane space	0.03058	SOD1
	GO:0031970	Organelle envelope lumen	0.03349	SOD1
	GO:0005730	Nucleolus	0.05439	BOP1, BYSL
	GO:0031981	Nuclear lumen	0.05554	BOP1, BYSL
	GO:0060205	Cytoplasmic vesicle lumen	0.05605	GSTP1
GO - molecular function	GO:0004128	Cytochrome-B5 reductase activity, acting on NAD(P)H	0.002498	NQO1
	GO:0030346	Protein phosphatase 2B binding	0.002498	SOD1
	GO:0016881	Acid-amino acid ligase activity	0.002997	GCLC
	GO:0003954	NADH dehydrogenase activity	0.003495	NQO1
	GO:0003723	RNA binding	0.003668	NQO1, BOP1, PRDX1, BYSL
	GO:0016653	Oxidoreductase activity, acting on NAD(P)H, heme protein as acceptor	0.004492	NQO1
	GO:0008432	JUN kinase binding	0.004492	GSTP1
	GO:0016655	Oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor	0.007476	NQO1

GO=Gene Ontology, ROS=Reactive oxygen species, SOD=Superoxide dismutase, HMOX1=Heme oxygenase-1

enrichment analysis are hepatocellular carcinoma, glutathione metabolism and fluid shear stress and atherosclerosis. PCOS, marked by chronic anovulation and hyperandrogenism, is closely linked to obesity and IR. These are key factors in non-alcoholic steatohepatitis, which can lead to cirrhosis with potential complications such as portal hypertension, liver failure and hepatocellular carcinoma.[36] Glutathione metabolism plays a dual role in cancer, offering both protection and promoting pathology. Elevated glutathione levels may shield tumour cells, conferring resistance to chemotherapy.[37] Women with PCOS display increased serum levels of homocysteine, glutathione, lipid peroxidation and superoxide, potentially affecting reproductive health and raising cancer risk.[38] Fluid shear stress activates the Ras-MEKK-JNK pathway, impacting endothelial gene expression in atherosclerosis-related diseases.[39] Disruptions in this pathway could potentially lead to cancer.

The hub genes selected from the PPI network of PCOS and EC include *RECQL4, RAD54L, ATR, CHTF18, WDHD1, CDT1, PLK1*, *PKMYT1, RAD18* and *RPL3*. Ribosomal protein S3 negatively modulates *RECQL4's* unwinding activity, influencing active DNA repair during cellular stress. *RECQL4*, crucial for preventing tumourigenesis and maintaining genome integrity, is upregulated in cancer.[40] *RAD54L*, involved in homologous recombination and DNA repair, is markedly upregulated, correlating with a worse prognosis in multiple cancers.[41] ATR, monitoring DNA structure, phosphorylates proteins in DNA damage response pathways. Truncating mutations in ATR are identified in endometrioid EC, producing a shortened or incomplete ATR protein.[42,43]

Based on the PPI network analysis of PCOS and OC, hub genes were identified, including *HMOX1, TXNRD1, NQO1, GCLC, GSTP1*, *PRDX1, SOD1, GPX3, BOP1* and *BYSL*. Heme oxygenase-1 (*HMOX1*) is a vital enzyme in heme breakdown. In endometriotic lesions, where endometrial tissue grows outside the uterus, macrophages infiltrate and play a crucial role in processing heme released during menstruation. *HMOX1*, also called HO-1, processes heme within macrophages and is elevated in endometriosis-associated OC.[44] Thioredoxin reductase 1 (*TXNRD1*) is a key element of the thioredoxin system, a significant cellular antioxidant defence. It aids in reducing thioredoxin, essential for neutralising ROS and sustaining proteins in a functional

Table 5: Pathway enrichment analysis of hub genes between polycystic ovary syndrome and endometrial cancer

Category	Pathway	*P*	Genes
Reactome 2022	Polo-like kinase-mediated events R-HSA-156711	0.00002690	PLK1, PKMYT1
	Cyclin A/B1/B2-associated events during G2/M transition R-HSA-69273	0.00006709	PLK1, PKMYT1
	Cell cycle R-HSA-1640170	0.0002033	CDT1, PLK1, CHTF18, PKMYT1
	Cell cycle, mitotic R-HSA-69278	0.001860	CDT1, PLK1, PKMYT1
	G2/M DNA replication checkpoint R-HSA-69478	0.002498	PKMYT1
	Phosphorylation of Emi1 R-HSA-176417	0.002997	PLK1
	Activation of NIMA kinases NEK9, NEK6, NEK7 R-HSA-2980767	0.003495	PLK1
	G2/M transition R-HSA-69275	0.003532	PLK1, PKMYT1
	Mitotic G2-G2/M phases R-HSA-453274	0.003609	PLK1, PKMYT1
	Mitotic telophase/cytokinesis R-HSA-68884	0.006482	PLK1
WikiPathway 2023 human	DNA IR damage and cellular response Via ATR WP4016	0.000007524	RECQL4, PLK1, ATR
	Cell cycle WP179	0.00002451	PLK1, PKMYT1, ATR
	Integrated cancer pathway WP1971	0.0002105	PLK1, ATR
	Androgen receptor network in prostate cancer WP2263	0.001287	PLK1, ATR
	NIPBL role in DNA damage Cornelia De Lange syndrome WP5119	0.003994	ATR
	ATR signalling WP3875	0.004492	ATR
	SMC1 SMC3 role in DNA damage Cornelia De Lange syndrome WP5118	0.005488	RAD18
	Gastric cancer network 2 WP2363	0.01540	CHTF18
	Cohesin complex Cornelia De Lange syndrome WP5117	0.01687	PLK1
	DNA replication WP466	0.02081	CDT1
KEGG 2021 human	Cell cycle	0.00002704	PLK1, PKMYT1, ATR
	Progesterone-mediated oocyte maturation	0.001085	PLK1, PKMYT1
	Oocyte meiosis	0.001796	PLK1, PKMYT1
	Homologous recombination	0.02032	RAD54L
	Fanconi anaemia pathway	0.02668	ATR
	p53 signalling pathway	0.03591	ATR
	FoxO signalling pathway	0.06362	PLK1
	Cellular senescence	0.07533	ATR
	Ribosome	0.07627	RPL3
	Human immunodeficiency virus 1 infection	0.1011	ATR

KEGG=Kyoto Encyclopaedia of Genes and Genomes, IR=Insulin resistance

state. Elevated metabolic activity in cancer cells results in increased oxidative stress, leading to the upregulation of *TXNRD1* in various cancer types.[45]

The identified hub genes from the analysis were used to predict potential drugs using the DSigDB database. The top three chemical molecules for the association between PCOS and EC were testosterone (CTD 00006844), calcitriol (CTD 00005558) and quercetin (CTD 00006679). For the association between PCOS and OC, the top drugs were 1-chloro-2,4-dinitrobenzene (CTD 00005848) and eugenol (CTD 00005949). Testosterone may contribute to EC through membrane-initiated signalling pathways. Steroid inhibitors could reduce hormone-dependent EC.[46] Calcitriol, the active Vitamin D form, may have anti-tumour effects through the VDR gene mechanism.[47] Quercetin inhibits endometrial fibrosis, offering potential in treatments and prevention.[48]

For the PCOS and OC association, 1-chloro-2,4-dinitrobenzene (DNCB) is linked to assessing biological risk in primary lung cancer.[49] Eugenol inhibits breast precancerous lesion progression through the HER2/PI3K-AKT pathway, showing promise for breast cancer treatment.[50] Cisplatin combined with eugenol effectively restrains OC growth, reducing side population cells and suppressing cancer stem cell resistance through the Notch-Hes1 pathway.[50] Figure 4 illustrates the schematic representation of our study.

Comparable research was done independently on PCOS with ovarian and EC.

Our findings diverge from theirs as their studies employed separate sample sets for each condition, while ours involved a simultaneous comparison of both types of cancer with PCOS, resulting in distinct outcomes.

Since our findings were obtained by pure bioinformatics analysis, the function of hub genes and prospective medicines is required to be further confirmed by scientific investigation *in vitro* and *in vivo*.

Table 6: Pathway enrichment analysis of hub genes between polycystic ovary syndrome and ovarian cancer

Category	Pathway	*P*	Genes
Reactome 2022	Cellular response to chemical stress R-HSA-9711123	1.784e-15	NQO1, GCLC, GPX3, TXNRD1, GSTP1, PRDX1, HMOX1, SOD1
	Detoxification of ROS R-HSA-3299685	2.614e-12	GPX3, TXNRD1, GSTP1, PRDX1, SOD1
	Cellular responses to stress R-HSA-2262752	1.172e-10	NQO1, GCLC, GPX3, TXNRD1, GSTP1, PRDX1, HMOX1, SOD1
	Cellular responses to stimuli R-HSA-8953897	1.366e-10	NQO1, GCLC, GPX3, TXNRD1, GSTP1, PRDX1, HMOX1, SOD1
	Nuclear events mediated by NFE2L2 R-HSA-9759194	1.965e-10	NQO1, GCLC, TXNRD1, PRDX1, HMOX1
	KEAP1-NFE2L2 pathway R-HSA-9755511	6.977e-10	NQO1, GCLC, TXNRD1, PRDX1, HMOX1
	Glutathione conjugation R-HSA-156590	0.0001405	GCLC, GSTP1
	TP53 regulates metabolic genes R-HSA-5628897	0.0007138	TXNRD1, PRDX1
	Phase II - conjugation of compounds R-HSA-156580	0.001241	GCLC, GSTP1
	Metabolism R-HSA-1430728	0.001819	NQO1, GCLC, TXNRD1, GSTP1, HMOX1
WikiPathway 2023 human	Oxidative stress response WP408	2.605e-15	NQO1, GCLC, GPX3, TXNRD1, HMOX1, SOD1
	NRF2 pathway WP2884	8.778e-14	NQO1, GCLC, GPX3, TXNRD1, GSTP1, PRDX1, HMOX1
	Nuclear receptors meta pathway WP2882	2.535e-11	NQO1, GCLC, GPX3, TXNRD1, GSTP1, PRDX1, HMOX1
	Photodynamic therapy induced NFE2L2 NRF2 survival signalling WP3612	2.777e-10	NQO1, GCLC, GSTP1, HMOX1
	Transcriptional activation by NRF2 in response to phytochemicals WP3	4.082e-8	NQO1, GCLC, HMOX1
	Selenium micronutrient network WP15	6.560e-8	GPX3, TXNRD1, PRDX1, SOD1
	NRF2 ARE regulation WP4357	1.586e-7	NQO1, GCLC, HMOX1
	Antiviral and anti-inflammatory effects of Nrf2 On SARS-CoV-2 pathway WP5113	4.016e-7	NQO1, GCLC, HMOX1
	One carbon metabolism and related pathways WP3940	0.000002081	GCLC, GPX3, SOD1
	Ferroptosis WP4313	0.000003690	GCLC, TXNRD1, HMOX1
KEGG 2021 human	Hepatocellular carcinoma	9.698e-7	NQO1, TXNRD1, GSTP1, HMOX1
	Glutathione metabolism	0.000002596	GCLC, GPXA, GSTP1
	Fluid shear stress and atherosclerosis	0.00003804	NQO1, GSTP1, HMOX1
	Pathways in cancer	0.00009084	NQO1, TXNRD1, GSTP1, HMOX1
	Ferroptosis	0.0001826	GCLC, HMOX1
	Peroxisome	0.0007315	PRDX1, SOD1
	Ubiquinone and other terpenoid-quinone biosynthesis	0.005488	NQO1
	Selenocompound metabolism	0.008469	TXNRD1
	Huntington disease	0.009682	GPX3, SOD1
	Amyotrophic lateral sclerosis	0.01350	GPX3, SOD1

KEGG=Kyoto encyclopaedia of genes and genomes, ROS=Reactive oxygen species, SOD=Superoxide dismutase, HMOX1=Heme oxygenase-1, TXNRD1=Thioredoxin reductase 1

Table 7: Prediction of top 10 candidate drugs for polycystic ovary syndrome and endometrial cancer

Drug name	*P*	Genes
Testosterone CTD 00006844	8.984e-9	RECQL4, WDHD1, CDT1, PLK1, RAD54L, CHTF18, PKMYT1, RAD18
Troglitazone CTD 00002415	2.183e-7	RECQL4, CDT1, PLK1, RAD54L, CHTF18, PKMYT1
Calcitriol CTD 00005558	3.127e-7	RECQL4, WDHD1, CDT1, PLK1, RAD54L, CHTF18, PKMYT1, RAD18
Enterolactone CTD 00001393	0.000002289	RECQL4, WDHD1, CDT1, PLK1, RAD54L, PKMYT1
COUMESTROL CTD 00005717	0.000004649	RECQL4, WDHD1, CDT1, PLK1, RAD54L, PKMYT1, RAD18
0297417-0002B PC3 DOWN	0.000005272	WDHD1, CDT1, PKMYT1
Quercetin CTD 00006679	0.00001277	RECQL4, WDHD1, CDT1, PLK1, RAD54L, CHTF18, PKMYT1, ATR
Resveratrol CTD 00002483	0.00004129	RECQL4, WDHD1, CDT1, PLK1, RAD54L, ATR
LITHOCHOLIC ACID BOSS	0.00007266	CDT1, PLK1
Prazosin hydrochloride BOSS	0.0001327	CDT1, RAD54L

Table 8: Prediction of top 10 candidate drugs for polycystic ovary syndrome and ovarian cancer

Drug name	*P*	Genes
Alpha-hexylcinnamaldehyde CTD 00002937	2.605e-15	NQO1, GCLC, GPX3, TXNRD1, HMOX1, SOD1
Cinnamyl alcohol CTD 00001006	4.579e-15	NQO1, GCLC, GPX3, TXNRD1, HMOX1, SOD1
Bandrowski's base CTD 00002216	9.018e-15	NQO1, GCLC, GPX3, TXNRD1, HMOX1, SOD1
1-chloro-2,4-dinitrobenzene CTD 00005848	1.803e-14	NQO1, GCLC, GPX3, TXNRD1, GSTP1, PRDX1, HMOX1, SOD1
CHLOROBENZENE CTD 00001495	4.118e-14	GPX3, TXNRD1, GSTP1, HMOX1, SOD1
CHEBI: 18224 CTD 00001728	6.053e-14	NQO1, GCLC, GPX3, TXNRD1, HMOX1, SOD1
Eugenol CTD 00005949	2.258e-13	NQO1, GCLC, GPX3, TXNRD1, GSTP1, HMOX1, SOD1
MANEB CTD 00006239	9.244e-13	NQO1, GCLC, TXNRD1, PRDX1, SOD1
Disulfiram CTD 00005860	6.882e-12	NQO1, GCLC, GPX3, TXNRD1, HMOX1, SOD1
Tert-butylhydroquinone CTD 00000961	7.979e-12	NQO1, GCLC, TXNRD1, GSTP1, HMOX1

SOD=Superoxide dismutase, HMOX1=Heme oxygenase-1, TXNRD1=Thioredoxin reductase 1

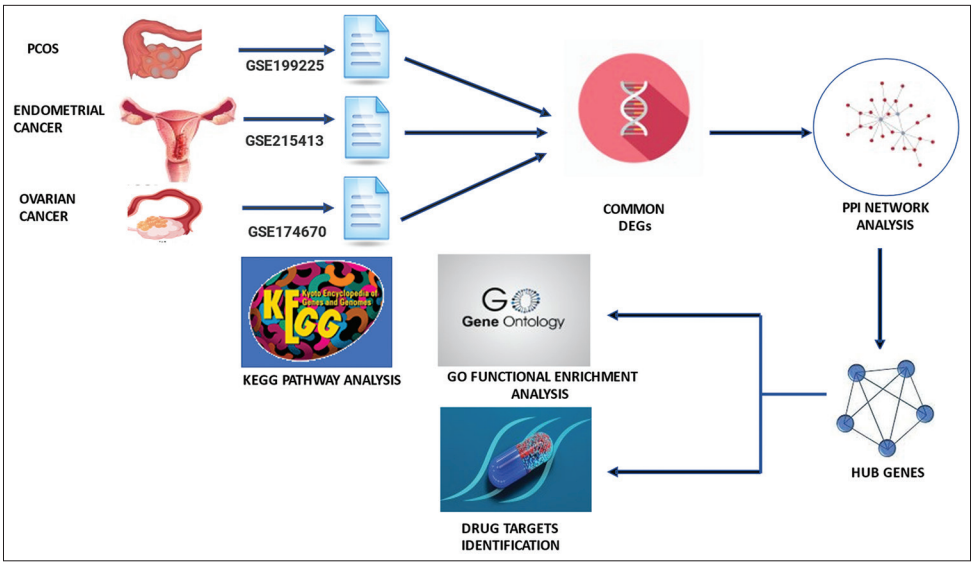

Figure 4: Research outline. PCOS = Polycystic ovary syndrome, DEGs = Differentially expressed genes, PPI = Protein–protein interaction

Conclusion

This study presents compelling evidence supporting the link between PCOS and endometrial and OC, with common DEGs identified through the screening of genome expression datasets. Bioinformatics analysis revealed gene signatures and regulatory patterns. In addition, we elucidated various molecular and GO pathways, offering a clear perspective on the genetic connection between EC and OC and PCOS. Furthermore, we identified potential small drug molecules associated with the hub genes. As our research relies on data, it is essential to conduct more experimental and clinical studies to confirm the findings of the study.

Authors contribution

Conception, design, collection, assembly data analysis and interpretation: KR, SQ. Manuscript writing: KR. This should be included in the file.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

All data utilised to support the conclusions of this study are publicly available from the NCBI GEO database with accession number GSE199225 (PCOS), GSE215413 (EC) and GSE174670 (OC).

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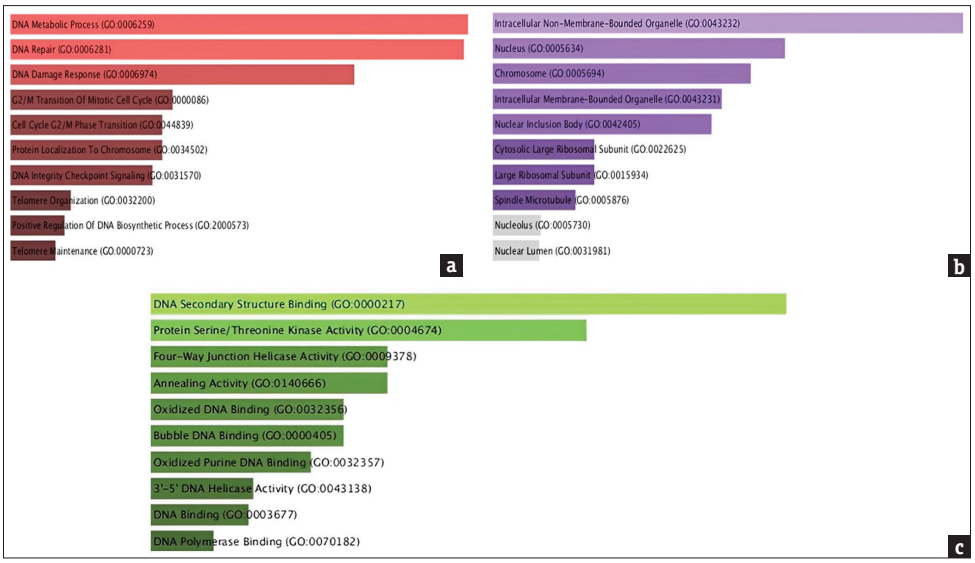
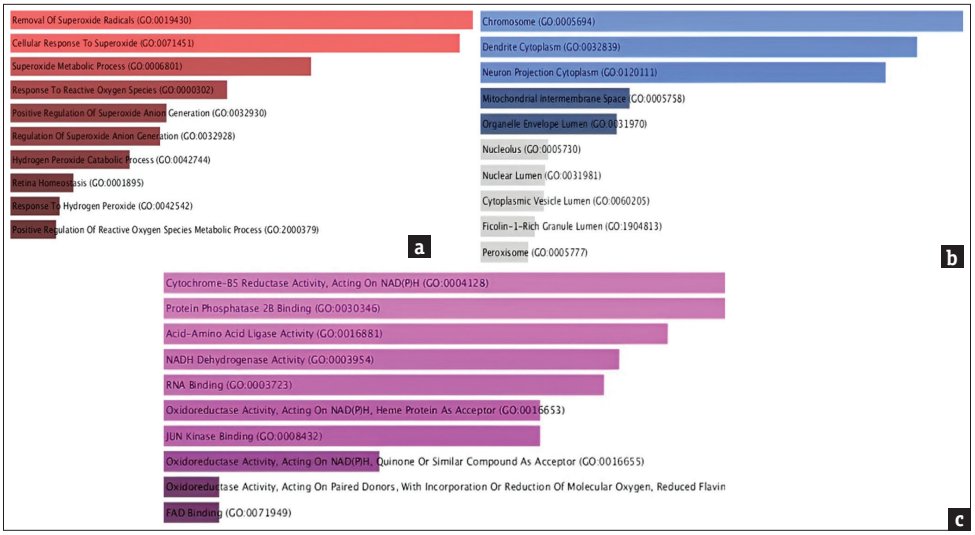
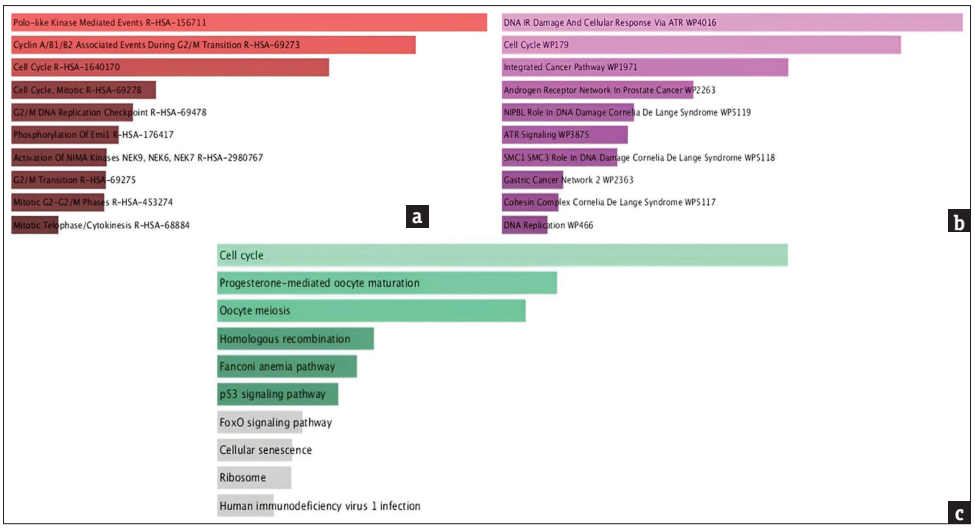


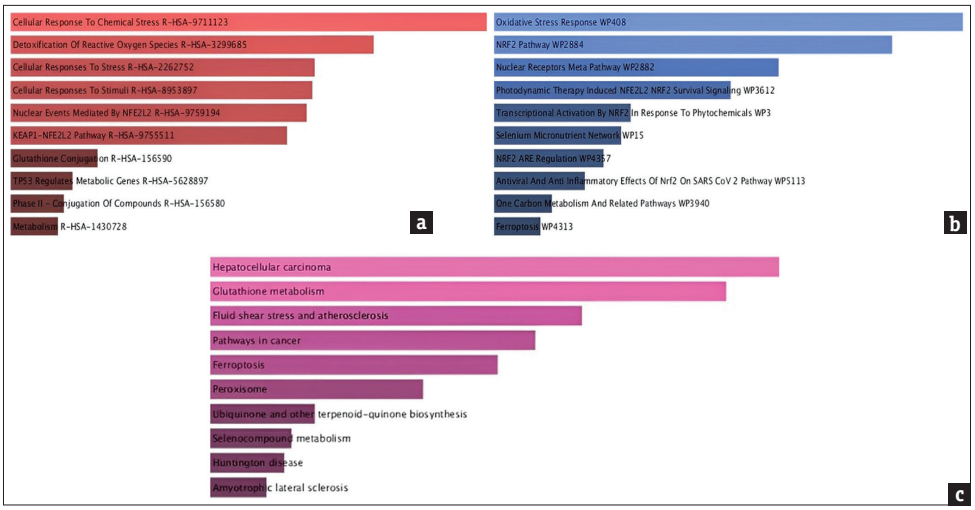
Supplementary Figure 1: Gene Ontology terms of Hub genes between polycystic ovary syndrome and endometrial cancer (a) Biological processes, (b) cellular component, (c) molecular function. GO = Gene Ontology



Supplementary Figure 2: Gene Ontology terms of hub genes between polycystic ovary syndrome and ovarian cancer (a) biological processes, (b) cellular component, (c) molecular function. GO = Gene Ontology



Supplementary Figure 3: Pathway enrichment analysis of hub genes between polycystic ovary syndrome and endometrial cancer. (a) Reactome pathway, (b) WikiPathway, (c) Kyoto Encyclopaedia of Genes and Genomes Human Pathway



Supplementary Figure 4: Pathway enrichment analysis of Hub genes between polycystic ovary syndrome and endometrial cancer. (a) Reactome pathway, (b) WikiPathway, (c) Kyoto Encyclopaedia of Genes and Genomes Human Pathway